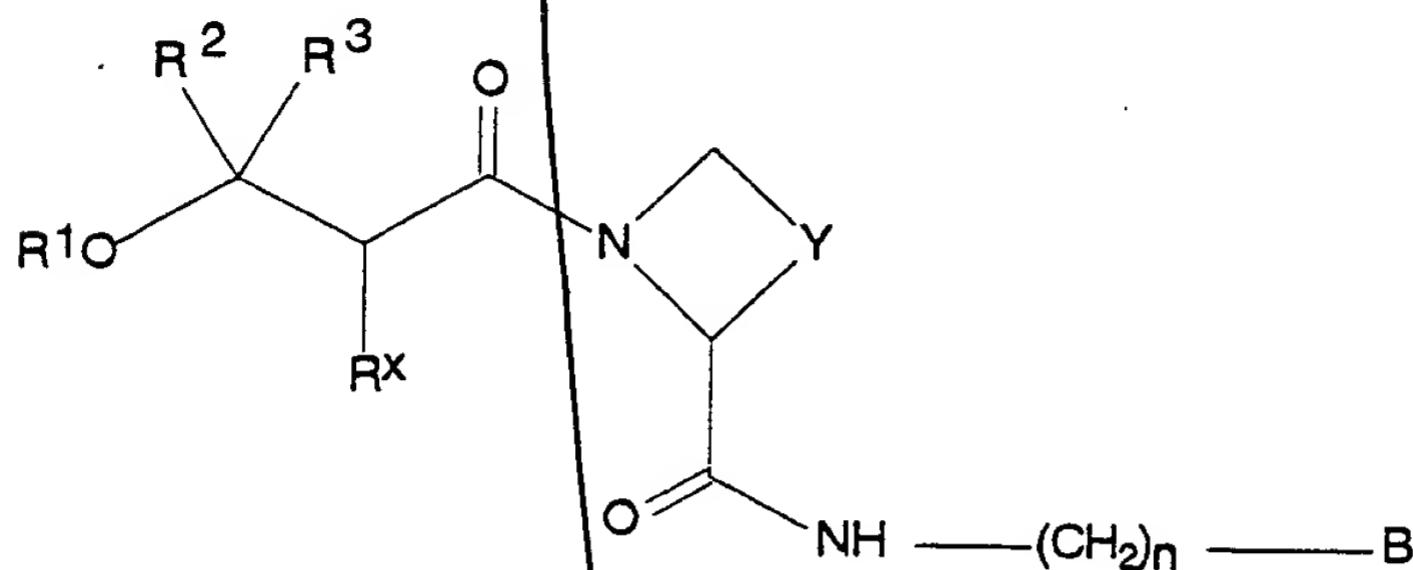


Claims

Sulf A II

1. A compound of formula I,

10



wherein

15 R^1 represents H, $C(O)R^{11}$, $SiR^{12}R^{13}R^{14}$ or C_{1-6} alkyl which latter group is optionally substituted or terminated by one or more substituent selected from OR^{15} or $(CH_2)_qR^{16}$;

R^{12} , R^{13} and R^{14} independently represent H, phenyl or C_{1-6} alkyl;

R^{16} represents C_{1-4} alkyl, phenyl, OH, $C(O)OR^{17}$ or $C(O)N(H)R^{18}$;

R^{18} represents H, C_{1-4} alkyl or $CH_2C(O)OR^{19}$;

20 R^{15} and R^{17} independently represent H, C_{1-6} alkyl or C_{7-9} alkylphenyl;

R^{11} and R^{19} independently represent H or C_{1-4} alkyl; and

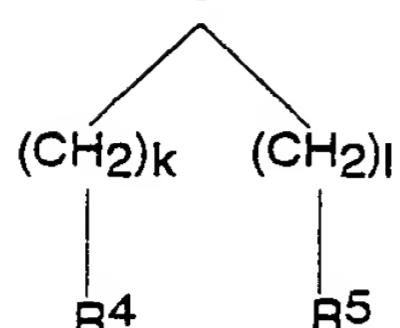
q represents 0, 1 or 2;

25 R^2 and R^3 independently represent H, C_{1-4} alkyl, cyclohexyl or phenyl;

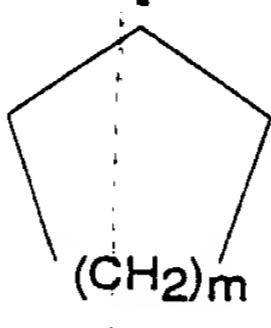
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R^x represents a structural fragment of formula IIa, IIb or IIc,

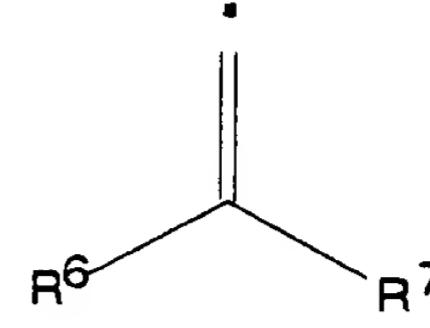
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IIa



IIb



IIc

wherein

k, l and m independently represent 0, 1, 2, 3 or 4;

10 R⁴ and R⁵ independently represent H, Si(Me)₃, 1- or 2-naphthyl, a polycyclic hydrocarbyl group, CHR⁴¹R⁴² or C₁₋₄ alkyl (which latter group is optionally substituted by one or more fluorine atoms), or C₃₋₈ cycloalkyl phenyl, methylenedioxyphenyl, benzodioxanyl, benzofuranyl, dihydrobenzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, 15 coumaranonyl, coumarinyl or dihydrocoumarinyl (which latter twelve groups are optionally substituted by one or more of C₁₋₄ alkyl (which latter group is optionally substituted by one or more halo substituent), C₁₋₄ alkoxy, halo, hydroxy, cyano, nitro, SO₂NH₂, C(O)OH or N(H)R⁴³); R⁴¹ and R⁴² independently represent cyclohexyl or phenyl;

20 R⁶ and R⁷ independently represent H, C₁₋₄ alkyl, C₃₋₈ cycloalkyl, phenyl (which latter group is are optionally substituted by one or more of C₁₋₄ alkyl (which latter group is optionally substituted by one or more halo substituent), C₁₋₄ alkoxy, halo, hydroxy, cyano, nitro, SO₂NH₂, C(O)OH or N(H)R⁴⁴) or together with the carbon atom to which they are attached form 25 a C₃₋₈ cycloalkyl ring;

R⁴³ and R⁴⁴ independently represent H or C(O)R⁴⁵; and

R⁴⁵ represents H, C₁₋₄ alkyl or C₁₋₄ alkoxy;

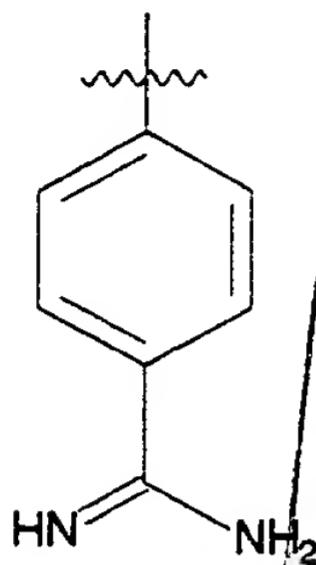
Y represents CH₂, (CH₂)₂, CH=CH, (CH₂)₃, CH₂CH=CH or CH=CHCH₂,

30 which latter three groups are optionally substituted by C₁₋₄ alkyl,

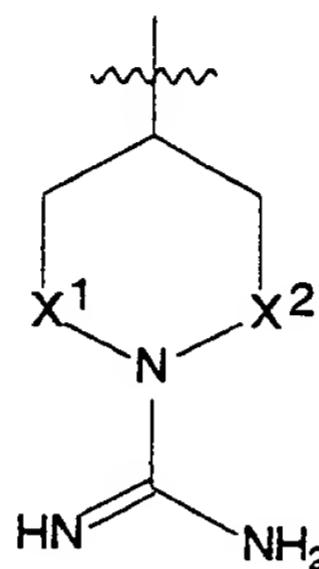
methylene, oxo or hydroxy;

n represents 0, 1, 2, 3 or 4; and

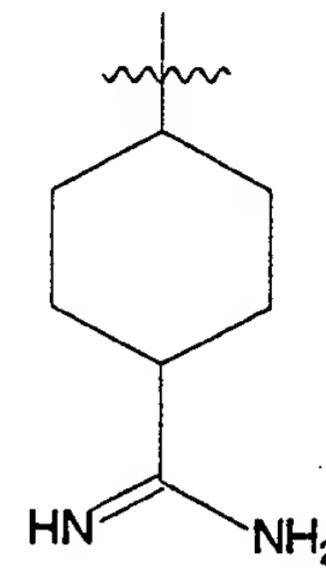
5 B represents a structural fragment of formula IVa, IVb or IVc



IVa



IVb



IVc

wherein

X¹ and X² independently represents a single bond or CH₂;

or a pharmaceutically acceptable salt thereof.

10

2. ~~A compound of formula I, as defined in Claim 1, wherein when n represents 2 and B represents a structural fragment of formula IVb, X¹ and X² do not both represent CH₂.~~

Sub A2
15 3. A compound of formula I, as defined in Claim 1 or Claim 2, wherein R¹ represents optionally substituted C₁₋₆ alkyl or H.

4. A compound of formula I, as defined in Claim 3, wherein R¹ represents H.

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5. A compound of formula I, as defined in any one of the preceding

Sub
A3

claims, wherein R^x represents a structural fragment of formula IIa.

6. A compound of formula I, as defined in any one of the preceding claims, wherein Y represents CH_2 or $(CH_2)_2$.

AB
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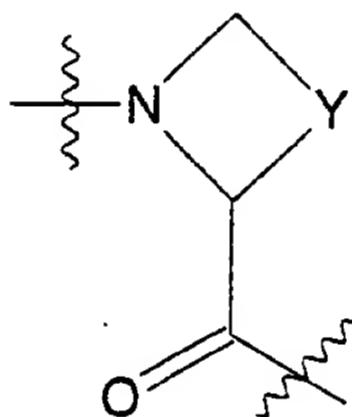
7. A compound of formula I, as defined in Claim 1 or any one of Claims 3 to 6, wherein n represents 1.

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8. A compound of formula I, as defined in Claim 1 or any one of Claims 3 to 7, wherein B represents a structural fragment of formula IVa.

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9. A compound of formula I, as defined in any one of the preceding claims, wherein the fragment



is in the S-configuration.

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10. A compound as claimed in Claim 1 which is
 (R) - $PhCH(CH_2OH)-C(O)-Aze-Pab$;
 (S) - $PhCH(CH_2OH)-C(O)-Aze-Pab$;
 (R) -3-methoxyphenyl- $CH(CH_2OH)-C(O)-Aze-Pab$;
25 (S) -3-methoxyphenyl- $CH(CH_2OH)-C(O)-Aze-Pab$;
 (R,S) -3,4-dimethoxyphenyl- $CH(CH_2OH)-C(O)-Aze-Pab$;
 (R) -2-naphthyl- $CH(CH_2OH)-C(O)-Aze-Pab$;
 (S) -2-naphthyl- $CH(CH_2OH)-C(O)-Aze-Pab$;
 (R) - $PhCH(CH_2OH)-C(O)-Aze-Pig$;
30 (S) - $PhCH(CH_2OH)-C(O)-Aze-Pig$;

(R,S) -PhCH(CH₂OH)-C(O)-Pro-(R,S)-Hig;
 (R) -2,5-dimethoxyphenyl-CH(CH₂OH)-C(O)-Aze-Pab;
 (S) -2,5-dimethoxyphenyl-CH(CH₂OH)-C(O)-Aze-Pab;
 (S) -3-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
5 (R) -3-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R,S) -3-aminophenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -3-(methylamino)phenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -3-(methylamino)phenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -PhCH(CH₂OH)-C(O)-Pro-Pab;
10 (R,S) -3,5-dimethylphenyl-CH(CH₂OH)-C(O)-Aze-Pab;
 (S) -3-(trifluoromethyl)phenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -3-(trifluoromethyl)phenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R,S) -3-hydroxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -((3-chloro-5-methylphenyl)-CH(CH₂OH)-C(O)-Pro-Pab;
15 (S) -((3-chloro-5-methylphenyl)-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -3-fluorophenyl-CH(CH₂OH)CO-Pro-Pab;
 (R) -3-fluorophenyl-CH(CH₂OH)CO-Pro-Pab;
 (S) -3-chlorophenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -3-chlorophenyl-CH(CH₂OH)-C(O)-Pro-Pab;
20 (R,S) -3,5-dimethylphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -3,5-bis(trifluoromethyl)phenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -3,5-bis(trifluoromethyl)phenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R,S) -3-methoxy-5-methylphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R,S) -(2,5-dimethoxyphenyl)-CH(CH₂OH)-C(O)-Pro-Pab;
25 (R,S) -(3,5-dimethoxyphenyl)-CH(CH₂OH)-C(O)-Pro-Pab;
 (R,S) -3,4-(methylenedioxophenyl)-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -3-(2-naphthyl)-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -3-(2-naphthyl)-CH(CH₂OH)-C(O)-Pro-Pab;
 (R,S) -3,5-dimethoxyphenyl-CH(CH₂OH)-C(O)-Aze-Pab;

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(R,S) -2-chloro-5-aminophenyl-CH(CH₂OH)-C(O)-Aze-Pab;
 (R) -3-methylphenyl-CH(CH₂OH)-C(O)-Aze-Pab;
 (S) -3-methylphenyl-CH(CH₂OH)-C(O)-Aze-Pab;
 (R) -2,5-dimethylphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -2,5-dimethylphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -3-methoxy-4-hydroxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -3-methoxy-4-hydroxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -3,5-dichlorophenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -3,5-dichlorophenyl-CH(CH₂OH)-C(O)-Pro-Pab;
10 (R) -2,3-dimethoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -2,3-dimethoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -3-methoxy-5-chlorophenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (S) -3-methoxy-5-chlorophenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R) -2-methyl-5-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
15 (S) -2-methyl-5-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab;
 (R,S) -Ph-C(Me)(CH₂OMe)-C(O)-Pro-Pab;
 (R) -2-chloro-3-methylphenyl-CH(CH₂OH)-C(O)-Aze-Pab;
 (S) -2-chloro-3-methylphenyl-CH(CH₂OH)-C(O)-Aze-Pab;
 (R) -2,3-(methylenedioxyphenyl)-CH(CH₂OH)-C(O)-Pro-Pab;
20 (S) -2,3-(methylenedioxyphenyl)-CH(CH₂OH)-C(O)-Pro-Pab; or
 (R,S) -Ph-C(Me)(CH₂OMe)-C(O)-Aze-Pab;
or a pharmaceutically acceptable salt thereof.

25 11. A compound of formula I, as defined in Claim 1, provided that when
R^x represents a structural fragment of formula IIa, then R⁴ and/or R⁵ (as
appropriate) do/does not represent phenyl substituted by halo-substituted
C₁₋₆ alkyl.

30 12. A compound of formula I, as defined in Claim 1, provided that when
R^x represents a structural fragment of formula IIa, then R⁴ and/or R⁵ (as

appropriate) do/does not represent methylenedioxophenyl, benzodioxanyl, benzofuranyl, dihydrobenzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, coumaranonyl, coumarinyl or dihydrocoumarinyl.

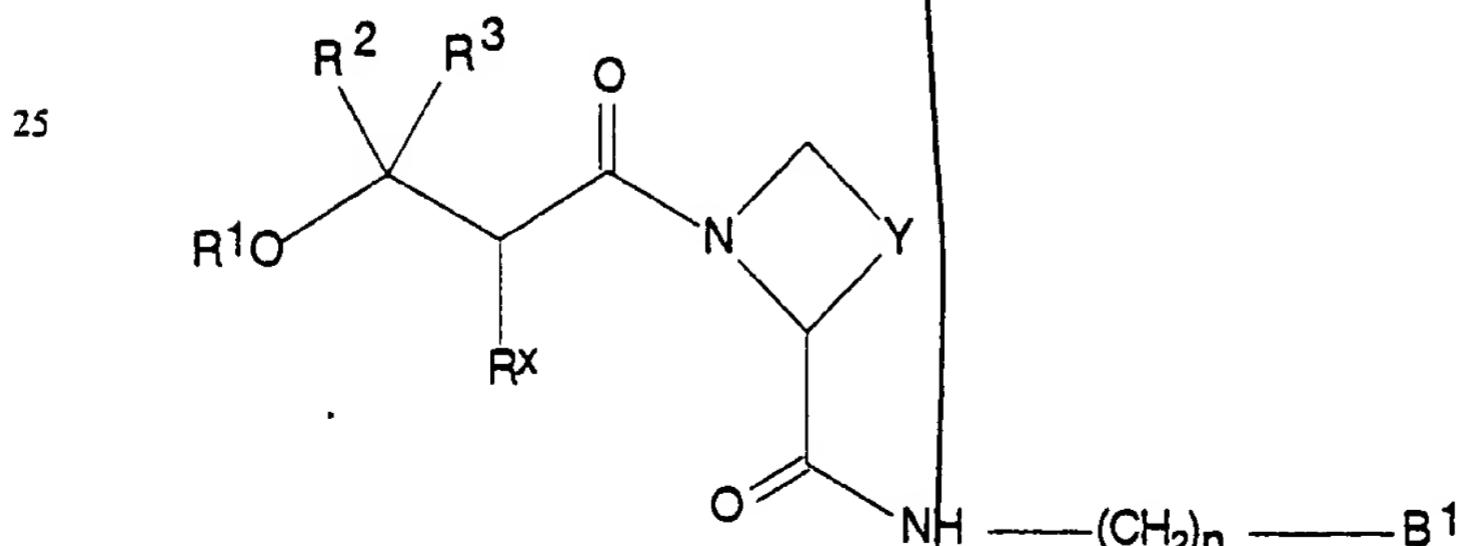
5 13. A compound of formula I, as defined in Claim 1, provided that when R^x represents a structural fragment of formula IIc, then R⁶ and/or R⁷ (as appropriate) represent(s) unsubstituted phenyl.

10 14. A compound of formula I, as defined in Claim 1, wherein, when R^x represents a structural fragment of formula IIa, then R⁴ and/or R⁵ (as appropriate) represent(s) phenyl substituted by halo-substituted C₁₋₆ alkyl.

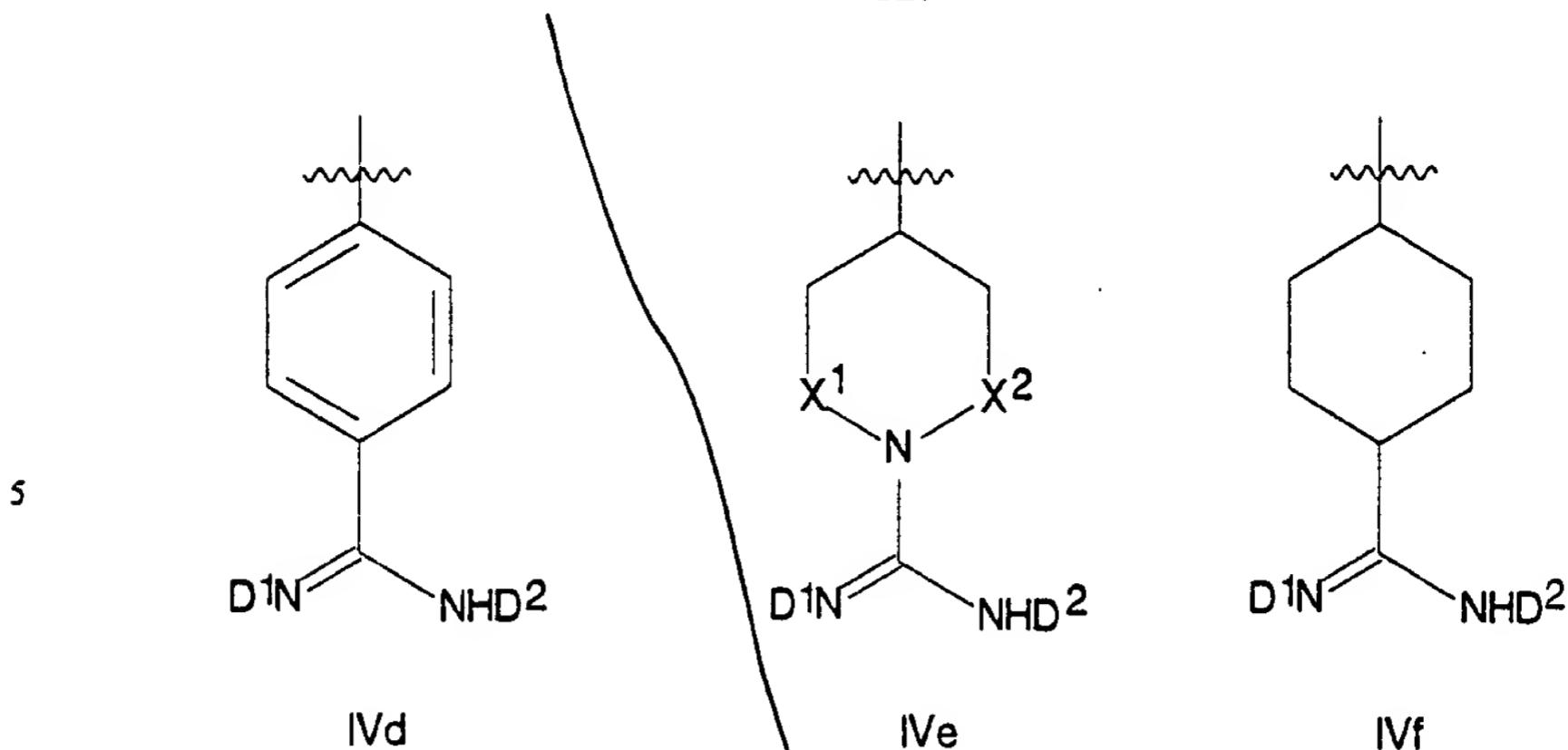
15 15. A compound of formula I, as defined in Claim 1, wherein, when R^x represents a structural fragment of formula IIa, then R⁴ and/or R⁵ (as appropriate) represent(s) methylenedioxophenyl, benzodioxanyl, benzofuranyl, dihydrobenzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, coumaranonyl, coumarinyl or dihydrocoumarinyl.

20 16. A compound of formula I, as defined in Claim 1, wherein, when R^x represents a structural fragment of formula IIc, then R⁶ and/or R⁷ (as appropriate) represent(s) substituted phenyl.

17. A compound of formula Ia,



30 wherein B¹ represents a structural fragment of formula IVd, IVe or IVf



wherein D¹ and D² independently represent H, OH, OR^a, OC(O)R^b,
10 OC(O)OR^c, C(O)OR^d, C(O)R^e and R^a, R^b, R^c, R^d and R^e independently
represent phenyl, benzyl, (CH₂)₂OC(O)CH₃ or C₁₋₆ alkyl which latter group
is optionally interrupted by oxygen; and R¹, R², R³, R^x, Y, n, X¹ and X² are
as defined in Claim 1, or a pharmaceutically acceptable salt thereof,
provided that D¹ and D² do not both represent H.

18. A compound of formula Ia, as defined in Claim 17, wherein D^1 represents H and D^2 represents OH, OCH_3 , $OC(O)R^b$ or $C(O)OR^d$ and R^b and R^d are as defined in Claim 17.

20 19. A compound as claimed in Claim 17 which is
(*R,S*)-Ph-CH(CH₂OH)-C(O)-Pro-Pab-OH;
(*R*)-3-methoxyphenyl-CH(CH₂OH)-C(O)-Aze-Pab-OH;
(*S*)-3-methoxyphenyl-CH(CH₂OH)-C(O)-Aze-Pab-OH;
(*S*)-3-methoxyphenyl-CH(CH₂OH)CO-Pro-Pab(Z);
25 (*R*)-3-methoxyphenyl-CH(CH₂OH)CO-Pro-Pab(Z);
(*S*)-3-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab-OH;
(*R*)-3-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab-OH;
(*S*)-3-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab-OC(O)Et;
(*R*)-3-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab-OC(O)Et;
30 (*S*)-3-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab-OC(O)CH₃;

130
(*R*)-3-methoxyphenyl-CH(CH₂OH)-C(O)-Pro-Pab-OC(O)CH₃;
(*R,S*)-3-Ph-C(Me)(CH₂OMe)-C(O)-Pro-Pab(Z); or
(*R,S*)-3-methylphenyl-CH(CH₂OAc)-C(O)-Pro-Pab-OMe;
or a pharmaceutically acceptable salt thereof.

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20. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

10 21. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

15 22. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

20 23. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of thrombosis.

24. A compound of formula I as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

25 25. The use of a compound I as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

30 26. The use as claimed in Claim 25, wherein the condition is thrombosis.

27. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of an anticoagulant.

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28. A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

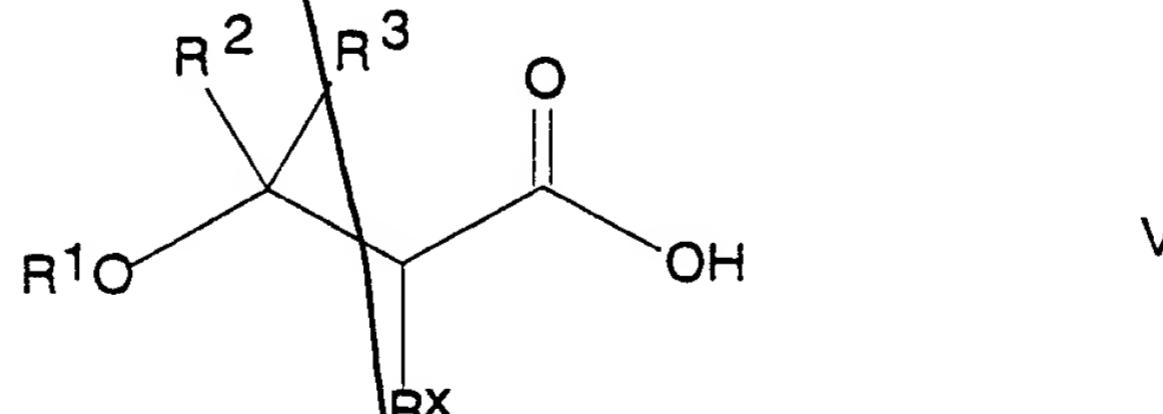
10 29. A method as claimed in Claim 28, wherein the condition is thrombosis.

30. A method as claimed in Claim 28, wherein the condition is hypercoagulability in blood and tissues.

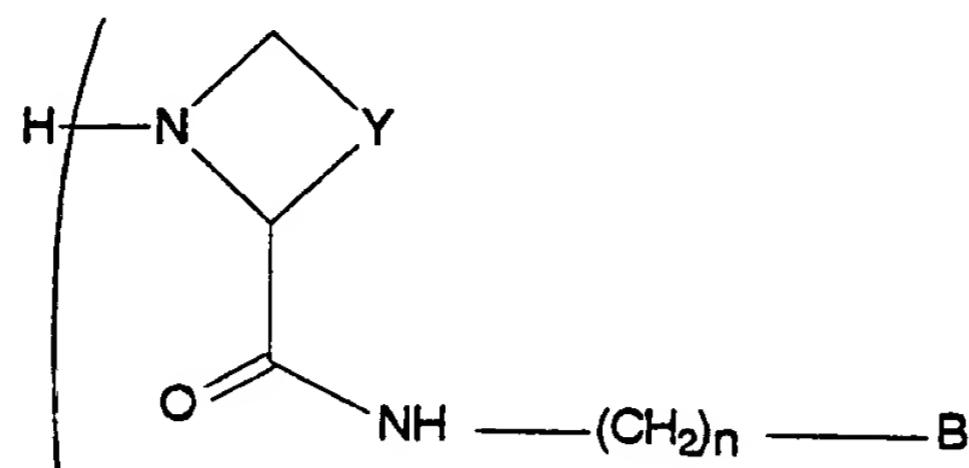
15 31. The use of a compound as defined in any one of Claims 17, 18 or 19 as a prodrug.

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PB* 20 32. A process for the preparation of compounds of formula I which comprises:

(a) the coupling of a compound of formula V,

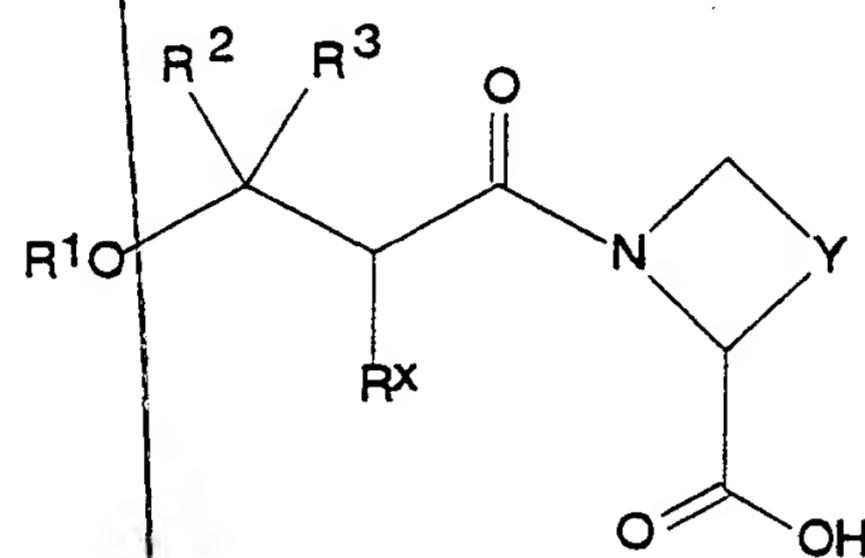


wherein R¹, R², R³ and R^x are as defined in Claim 1, with a compound of formula VI,



wherein Y, n and B are as defined in Claim 1; or

(b) the coupling of a compound of formula VII,



15 wherein R¹, R², R³, R^x and Y are as defined in Claim 1 with a compound of formula VIII,



VIII

wherein n and B are as defined in Claim 1.

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